IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: JUERG LAREIDA

Serial No.: 10/088,113

Filed: March 15, 2002

For: **MEDICAMENT FOR TREATMENT OF NEUROPATHIES**

Attorney Docket No. 29342/38562

Group Art Unit: 1617

Examiner: Jennifer M. Kim

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dated: September 6, 2006

James J. Napoli
Registraton No. 32,361
Attorney for Applicant

DECLARATION OF DR. JUERG LAREIDA PURSUANT TO 37 C.F.R. §1.131

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, JUERG LAREIDA, hereby state as follows:

1. I am the sole inventor of the subject matter claimed in the above-identified patent application.

2. I make this declaration for the purpose of providing evidence that the treatment of a neuropathy by application of sildenafil to a patient in need thereof, as recited in the claims of the above-identified patent application, was reduced to practice in Switzerland at least as early as September 29, 1999.

3. The attachment hereto, Exhibit A, is a copy of a note, hand signed by me, and is dated at least as early as September 29, 1999.

4. The note is in German with my stamped address on top.

5. The date on the note of Exhibit A has been deleted, but it is prior to the September 30, 1999, the filing date of provisional U.S. patent application No. 60/157,148, and the earliest date upon which DuBois U.S. Patent No. 6,399,601 can rely upon for priority.

6. The English-language translation of the note of attached Exhibit A is as follows:

> "Novel indication of Sildenafil (Viagra©)
>
> Sildenafil is patented as a therapeutic agent for coronary diseases, in the area of erectile dysfunction, and in case of irregular intestine mobility (i.e. Colon irritable). It seems to turn out that Sildenafil is effective in the area of peripheral nerves too in that nerves already damaged (i.e. peripheral diabetic polyneuropathy, gastroparesis) may exhibit their normal conductivity again and recuperate their function or improve the latter, respectively. It is not to be excluded that etiologically different neuropathies will react favourably to Sildenafil. Dosage is not clear but should be about at 10-50 mg per day."

7. The note has been maintained as a business record in the normal course of business.

8. The note illustrates the treatment of neuropathies using sildenafil.

9. The attachment hereto, Exhibit B, is patient's log sheets relating to treatment of the patient using Viagra. The attachment includes my notes concerning date of treatment, symptoms, and administered medication.

10. The dates on the pages of Exhibit B have been deleted, but are prior to September 30, 1999, the filing date of provisional U.S. patent application Serial No. 60/157,148, the earliest date upon which DuBois U.S. Patent

No. 6,399,601 can rely upon for priority. The personal data relating to the identity of the patient also has been deleted.

11. Exhibit B is in German and each page contains my stamp.

12. The sequence of events in the treatment described in the pages Exhibit B is as follows, with an English translation and specific dates omitted:

"prob. Viagra 50": 50 milligrams of Viagra has been prescribed for the patient in question;

"Erdbeeren": strawberries;

"Seit Viagra Ø kalten Füsse mehr! Neuropathie besser! Effekt von Viagra?!": Since Viagra no cold feet any longer. Neuropathy improved. Effect of Viagra?!;

"Rp alles": all medication;

"Viagra 100": 100 mg Viagra;

"Kopie der Krankengeschichte": copy of patient's history, which is hand signed by me.

13. Exhibit B shows a reduction to practice date prior to September 30, 1999, on which date a neuropathy patient, having problems relating to ingesting strawberries, contacted me and I found that the patient's neuropathy improved as a result of the sildenafil treatment.

14. Exhibits A and B demonstrate the successful reduction to practice of the method of treating neuropathies as recited in the claims of the above-identified patent application, at least as early as September 29, 1999.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the above-referenced patent application and any patent issued therefrom.

Date: 23.8.06

By: Juerg Lareida

glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; α2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; Other insulin secretagogues: linogliride, A-4166; glitazones: ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone; PPAR-gamma agonists; fatty acid oxidation inhibitors: clomoxir, etomoxir; α-glucosidase inhibitors: acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; β-agonists: BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243; phosphodiesterase inhibitors: L-386,398; lipid-lowering agents: benfluorex; antiobesity agents: fenfluramine; vanadate and vanadium complexes (e.g. Naglivan®) and peroxovanadium complexes; amylin antagonists; glucagon antagonists; gluconeogenesis inhibitors; somatostatin analogs and antagonists; antilipolytic agents: nicotinic acid, acipimox, WAG 994. Any combination of agents can be administered as described above.

In addition to the categories and compounds mentioned above, the compounds of the present invention can be administered in combination with thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors, or sorbitol dehydrogenase inhibitors, or combinations thereof, to treat or prevent diabetes, insulin resistance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, particularly myocardial ischemia.

It is generally accepted that thyroid hormones, specifically, biologically active iodothyronines, are critical to normal development and to maintaining metabolic homeostasis. Thyroid hormones stimulate the metabolism of cholesterol to bile acids and enhance the lipolytic responses of fat cells to other hormones. U.S. Patent Numbers 4,766,121; 4,826,876; 4,910,305; and 5,061,798 disclose certain thyroid hormone mimetics (thyromimetics), namely, 3,5-dibromo-3'-[6-oxo-3(1H)-pyridazinylmethyl]-thyronines. U.S. Patent Number 5,284,971 discloses certain thyromimetic cholesterol lowering agents, namely, 4-(3-cyclohexyl-4-hydroxy or -methoxy phenylsulfonyl)-3,5 dibromo-phenylacetic compounds. U.S. Patent Numbers 5,401,772; 5,654,468; and 5,569,674 disclose certain thyromimetics that are lipid

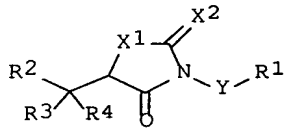
Exhibit B

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN 884328-54-5 REGISTRY
ED Entered STN: 15 May 2006
CN L 386398 (9CI) (CA INDEX NAME)
ENTE A phosphdiesterase inhibitor
MF Unspecified

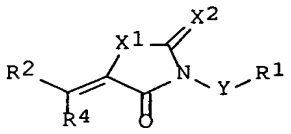
L2 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2006:367143 HCAPLUS Full-text
TI Rhodanine derivatives as PPAR receptor modulators and their preparation, pharmaceutical compositions and use for treatment and prophylaxis of various diseases
IN Sarshar, Sepehr; Marappan, Subrumanian
PA Auspex Pharmaceuticals, Inc., USA

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2006041921	A2	20060420	WO 2005-US35832	20051004
PRAI	US 2004-616574P	P	20041005		

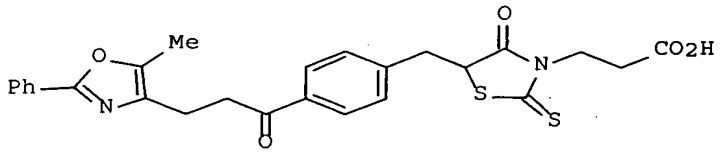
OS MARPAT 144:412493
GI



I



II



III

AB Processes for the prepn. of compds. of formulas I and II are described. These compds. can be used as PPAR modulators and for the treatment and/or management of cancer, inflammation, cellular differentiation and proliferation, wound healing, metabolism of lipids and carbohydrates, obesity, diabetes, and energy homeostasis. Compds. of formula I and II wherein X1 and X2 are independently O, S, or NH; Y is (un)substituted C1-10 alkyl; R1 is (un)substituted C5-11 oxocycloalkenyl, (R9CO)(R10CO)CH, or (un)substituted dioxodioxanyl; R9 and R10 are independently OH, alkoxyl, aryloxy, NH2, alkylamino, arylamino, N-aryl-N-alkylamino, -NHNH2, alkylhydrazino, arylhydrazino, N-aryl-N-alkylamino, NHOH and derivs., alkyl, or aryl; R2 and R3 are independently H, halo, or alkyl; R4 is substituted aryl and heteroaryl; and their pharmaceutically acceptable salts, and prodrugs thereof are claimed. Example compound III was prepared by addition of methyllithium to 4- (diethoxymethyl)benzaldehyde to give the corresponding alc., which was oxidized to give 4-(diethoxymethyl)acetophenone, which underwent acylation with di-Et carbonate; the resulting 2-[4-(diethoxymethyl)benzoyl]acetate underwent alkylation with 4-chloromethyl-5-methyl-2-phenyloxazole followed by decarboxylation to give 4-[3-(5-methyl-2-phenyl-4-oxazolyl)propionyl]benzaldehy de, which underwent condensation with rhodanine-N-propionic acid to give 4-[3-(5-methyl-2-phenyl-4-oxazolyl)propionyl]benzylidene-3-(β-carboxyethyl)rhodanine, which underwent hydrogenation to give example compound III. The invention compds. were evaluated for their PPAR-γ modulating activity. From the assay, it was determined example compound III exhibited an EC50 0.127 μM.

IT 884328-54-5, L 386398
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of rhodanine derivs. as PPAR receptors modulators useful in treatment and prophylaxis of diseases)

Exhibit A

Dr.med.J.Lareida
Endokrinologie & Diabetologie FMH
Vordere Vorstadt 16
5000 Aarau

Neue Indikation von Sildenafil (Viagra®)

Sildenafil ist patentiert als Koronartherapeutikum, im Bereich der erektilen Funktion und bei Motilitätsstörungen des Darmes (i.e.Colon irritabile). Es scheint sich herauszustellen, dass Sildenafil auch im Bereich der peripheren Nerven wirkt, indem bereits geschädigte Nerven (i.e. periphere, diabetische Polyneuropathie, Gastroparese) nach Applikation mit Sildenafil wieder eine normale Leitfähigkeit aufweisen können und somit ihre Funktion wieder wahrnehmen respektive verbessern können. Es ist nicht ausgeschlossen, dass auch aetiologisch unterschiedliche Neuropathien auf Sildenafil günstig reagieren. Die Dosierung ist unklar, dürfte jedoch etwa bei 10-50mg tgl liegen.

Dr.med.J.Lareida

Exhibit B

	prob. Viagra vo
Gd Beeren	
Seit Viagra ∅ kalten Füsse mehr! Neuropathie besser!	Rp alles
> Effekt von Viagra?!	?! Viagra 100

Dr. med. Jürg Lareida
...ere Medizin
...Endokrinologie
...ordere Vorstadt 16
5000 Aarau

Kopie der Krankengeschichte

BEST AVAILABLE COPY

0628232718

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Tel. 062 / 822 27 66

Sermion 3x1
Hytrin BPH 1.0.0
Diamicron 1.0.1
Inflamac 1.R
Aspirin cardio
Vibrocil Gel

Inflixi

Diamicron
Aspirin cardio
Inflamac 1.R
Sermion 2x1

Diamicron 1.0.0
Aspirin cardio
Sermion
Zocor 0.0.1
Viagra

Rp Inflamac SR

Viagra

Effekt von Viagra?!

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